Increase Production Efficiencies With Single-Use Transfer Lines

Presterilized single-use systems reduce the time necessary for cleaning and validation of processing equipment and reduce the risk of cross contamination.

BY JOHN BOEHM

Manufacturers across industries rely on innovative technology to meet two critical production requirements: speed and cost-efficiency. Biopharmaceutical manufacturers understand this concept and are implementing new ways to leverage existing plant infrastructure to enhance process reliability and flexibility. One solution that continues to gain momentum is single-use systems — particularly single-use transfer lines — which can deliver significant value through added flexibility, improved asset/equipment utilization, and increased cost savings.

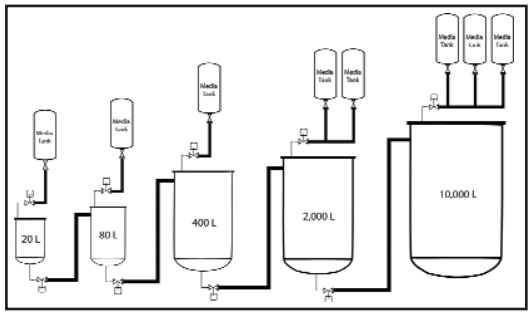

Diagram 1: A traditional stainless steel process for seed train scale-up

Initially, single-use systems that gained market acceptance consisted of tubing, bags, filters, and connectors. Bioprocessing facilities used these systems for process storage applications and sterile cell culture media. Single-use bioreactors then entered the market in research and development labs and rapidly moved into pilot plants and larger scale production facilities as integral systems for production and seed train scale-up.

Now, single-use transfer lines are used throughout the bioprocess to reduce operational costs. Unlike hard piping, the flexible tubing in single-use transfer lines does not require expensive and time-consuming cleaning and validation. Manufacturers can manage business cycles by quickly changing process steps or converting to a new product — a key advantage for multiple product facilities in which process requirements change with the drug being produced. Innovative manufacturers now incorporate single-use transfer lines in seed trains, suite-to-suite transfer, and final-fill applications.

Benefits Of Single-Use Systems

Single-use transfer lines reduce the downtime associated with cleaning and validating the processing equipment, allowing manufacturers to boost productivity and accelerate time to market. Between each production batch, fixed tubing and reusable valves need to be cleaned to maintain desired sterility. Single-use systems are presterilized, helping to eliminate traditional cleaning and sterilization. A single-use system gets the process up and running sooner and increases output without the entire process being placed on hold for validation. Manufacturers save costs in the labor, chemical, water, and energy demands associated with cleaning and validation. Single-use systems also improve the safety of drug development and delivery. Presterilized, single-use assemblies reduce the risk of cross contamination that may lead to product loss or reduced yields. This benefit is further magnified for companies that produce multiple products within single facilities.

Single-Use Systems For Seed Trains

Modern bioprocessing facilities feature production bioreactors with capacities of 5,000 L, 10,000 L, and even 25,000 L. Scaling up inoculum from a few million cells in several milliliters of culture to these production volumes is a challenge that requires aseptic transfer at each point along the seed train. Traditional bioprocessing facilities accomplish scale-up using a dedicated series of stainless steel bioreactors linked together with valves and rigid tubing (see *diagram 1*).

To prevent contamination between production runs, a clean-in-place (CIP) system is included in each bioreactor, vessel, and piping line to remove any residual materials. A steam-in-place (SIP) system, consisting of steam pipes, temperature sensors, and condensate collection piping, provides sterility assurance at the start of each culture. These CIP and SIP systems require extensive validation testing, and the valves and piping contained in these systems can create additional validation challenges. In addition, CIP and SIP systems must be revalidated after significant maintenance or changes to connecting piping and

valves networks. Bioprocess engineers can replace most storage vessels and fixed piping networks with single-use storage systems and transfer lines. Single-use systems eliminate the need for CIP validation for many components and reduce maintenance and capital expense by eliminating expensive vessels, valve, and sanitary piping assemblies.

Diagram 2 depicts a 10,000 L production suite, which relies on stainless steel bioreactors but integrates single-use technology for cell culture media storage and key transfer lines.

Single-use media storage systems are routinely manufactured for volumes ranging from 20 L to 2,500 L. Media storage systems arrive at the bioprocess facility sterilized by gamma irradiation and are often fitted with integrated filters, sampling systems, and connectors. Using a single-use SIP connector allows operators to make sterile connections between these presterilized single-use systems and stainless steel bioreactors for aseptic transfer of media.

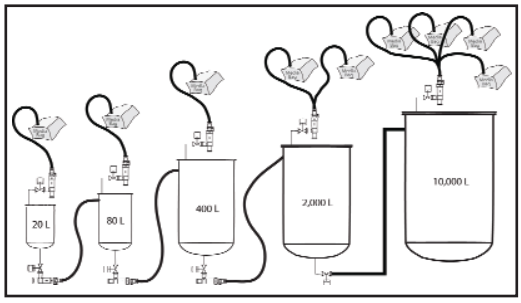

Diagram 2: A seed train set up using stainless steel bioreactors and single-use media bags and transfer lines

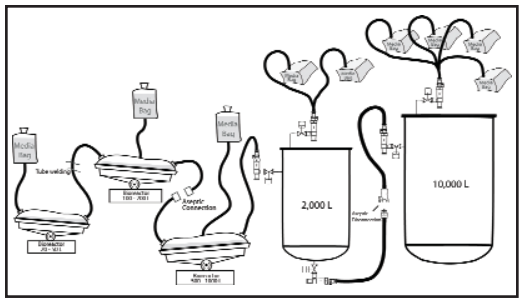

Diagram 3: A model facility that incorporates single-use media storage and bioreactors using stainless-steel bioreactors for the two largest vessels of 2,000 L and 10,000 L

Similarly, operators can use single-use transfer lines to transfer inoculum between bioreactors, using either a peristaltic pump or head-space pressure for flow rates up to 30 L per minute. Such transfer lines can reduce the number of reusable valves required for transfer and can eliminate problem areas for CIP and SIP validation. Terminating each presterilized transfer line with a single-use SIP connector provides sterility assurance equal to that of traditional fixed piping at lower capital costs. With the acceptance of single-use bioreactors, some bioprocess engineers are using these systems for seed trains and small scale productions. Single-use bioreactors range in volume from 1 L to 1,000 L and use two different modes of mixing: rocking platform and impeller. Rocking platform bioreactors consist of pillow-style bags secured to a tray mounted on pneumatic lifters. Impeller-based single-use bioreactors are based on three-dimensional "drum" bags fitted with a single-use impeller before sterilization. These systems are connected to a cell culture media storage bag — either by aseptic welding or aseptic connectors — using flexible tubing.

Likewise, flexible tubing with aseptic connections is used for transfer lines between each reactor in the process. For production volumes over 1,000 L, a single-use bioreactor must ultimately seed one or more stainless steel bioreactors. SIP connectors incorporated into the single-use bioreactor design can link the single-use and stainless steel section of a seed train. For added safety, a quick-disconnect coupling that has been validated as an aseptic disconnect can be used to remove single-use bags and tubing after the media transfer is complete. *Diagram 3* shows a model facility that incorporates single-use media storage and bioreactors, using stainless steel bioreactors for the two largest vessels of 2,000 L and 10,000 L.

Single-Use Systems For Suite-To-Suite Transfer

After completing the upstream production, the protein-containing medium must be aseptically transferred to a different location in the production facility in preparation for the final filling operation. This suite might be located in a room next door or much farther away. Traditional bioprocessing facilities accomplish this transfer by using stainless steel manifolds with piping or reusable hoses as transfer lines. This equipment requires validated CIP systems and/or washing procedures prior to use and sterilization before each media transfer.

Process engineers are now incorporating single-use transfer lines between the bioreactor in the process suite and the transfer vessel. Using presterilized connectors and tubing, the medium can be moved from the production suite to the preparation suite without the need to sterilize stainless steel piping or equipment.

In addition to faster production, single-use systems allow the manufacturer greater flexibility when determining which process to run in each production suite. The enhanced mobility eliminates many of the restrictions that hard-plumbed piping can place on the manufacturing facility. In addition, disconnecting transfer lines using a single-use valved coupling enables the processor to make an aseptic disconnection from the bioreactor without the risk of product contamination.

The risk of cross contamination in the suite-to-suite transfer process is high, especially in multiproduct facilities, and can potentially lead to product loss or reduced production yields. Presterilized, single-use assemblies reduce these risks and improve the speed and safety of drug development and delivery. Disconnecting the transfer lines aseptically assures that the product has not been compromised during production.

Single-Use Systems In The Final Fill Operation

The final step in the production process is transferring the new medium from the transfer vessel or bags and into smaller vials, bottles, or containers for distribution. Traditionally, the final fill operation includes stainless steel equipment connected via reusable valves, rigid tubing, and steel pipes. Again, this

equipment requires validation and must be subjected to a CIP cycle after each filling cycle. Today, many process engineers are designing this operation with single-use transfer lines in place of stainless steel equipment to reduce sterilization time and cost.

Using single-use systems during a final fill operation can eliminate the use of three-way valve assemblies in mobile stainless steel transfer tanks. Final fill tanks are designed to transfer formulated product from formulation suites to storage areas and ultimately to filling suites. To allow sterile connection to and from these vessels, designers traditionally add the three-way valve assemblies, which fill and drain ports. The design of these three-way valves makes it difficult to validate cleaning procedures.

In addition, they require regular maintenance and may add significant weight to mobile vessels, especially in tanks with multiple inlet and outlet ports. Replacing these three-way valve assemblies with single-use transfer lines and connectors eliminates cleaning validation and maintenance while reducing mobile vessel weight by tens of kilograms.

Single-use transfer lines can be attached before vessel SIP sterilization with SIP connectors (used as either steam access or condensate drainage sites) or can be steamed separately before fluid transfer. For vessel outlet, combining a number of single-use components into the transfer line can create a robust system to ensure product safety. For example, outlet transfer lines could incorporate a single-use SIP connector to attach to the sterile holding tank. In this case, a "through-the-wall" fluid transfer system brings a portion of the transfer line into an isolator where filling occurs. Next, a quick-connect fitting or aseptic connector attaches the transfer line to the filling machine. Finally, transfer lines using a valved quick-disconnect coupling aseptically disconnect the processor from the filling equipment.

As more manufacturers take advantage of the benefits of single-use systems, integration of these systems with traditional stainless steel equipment will continue to grow. Increasing the speed and cost-efficiency of the production process while maximizing existing facilities and equipment can have a significant bottom-line impact for biotech start-ups and large-scale manufacturers. Single-use transfer lines are a proven option for manufacturers to save time and reduce cost. ■

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